Alan Goldhammer, PhD
Associate Vice President,
US Regulatory Affairs

PhRMA

July 6, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2004D-0188: Draft Guidance for Industry on Development and Use of Risk Minimization Action Plans (69 Federal Register 25130; May 5, 2004)

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies. Our member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives; our members invested over $32 billion during 2003 in the discovery and development of new medicines.

Members of PhRMA share a mutual interest with FDA in bringing safer and more effective products to the market as rapidly as possible, and we embrace the importance of minimizing the occurrence of avoidable adverse events. Bringing a new drug to the market requires considerable commitment of time and resources. In order for industry to appropriately design and execute efficient drug development programs, it is important that the Agency ensure that its policies and expectations are transparent to all stakeholders, and that the standards are consistently applied. The three draft guidance documents on pre-marketing risk assessment, development and use of Risk Minimization Action Plans (RiskMAPs), and good pharmacovigilance practices represent significant progress towards these goals. When finalized, the three guidance documents will provide a good framework for the Agency and industry in their risk management efforts. PhRMA appreciates the opportunity to provide comments on the draft guidance documents.

PhRMA member companies are pleased to see that the Agency has significantly revised the guidance documents to incorporate the public input on the risk management concept papers that were published last year (68 Federal Register 11120; March 7,2003). We strongly support the development of concept papers and recommend that this approach be utilized routinely for development of major guidance documents that may precipitate extensive comments from interested parties. PhRMA agrees with and supports most of the concepts outlined in the draft guidance documents, particularly the over-arching philosophy that the ultimate goal of risk management is to ensure that risk management efforts are directed to effective processes that achieve a positive benefit/risk balance for patients. We are pleased to see increased reference to the balance between benefits and risks throughout the documents, as well as acknowledgment that RiskMAPs should be used judiciously, so as not to interfere with the delivery of benefit to the patient. This concept should also apply to pre-marketing risk assessment and post-marketing pharmacovigilance activities. Any activity beyond current regulatory requirements should be carefully assessed to ensure that it will provide meaningful

2004D-0188 C 8

benefit relevant to the patient population at risk, and not delay or hinder patient access to new effective therapy.

PhRMA is also encouraged to see that FDA has incorporated into all three draft guidance documents the concept that a number of different stakeholders must collaborate with industry and the Agency in risk management activities if significant improvement in the overall benefit/risk balance is to be achieved.

Since many of PhRMA's members are multinational companies, we also applaud the Agency's efforts to conform with internationally harmonized definitions and standards as much as possible. FDA guidance documents should be aligned with the approach developed by ICH and CIOMS to ensure that risk management can be a global process, as is appropriate for global products. The basic structure of risk management documents should be similar globally to allow use of the same document for all countries whenever possible. This increases the transparency and consistency of implementation of agreed post-marketing commitments. It would be useful for FDA to highlight in the guidance documents the important differences from ICH and EU guidance documents, the rationale for these differences, and the steps being taken to harmonize the differences. We believe that a global approach to pharmacovigilance and risk management is extremely important, and we strongly encourage FDA to harmonize with international consensus initiatives.

During public presentations regarding the risk management concept papers, FDA representatives have noted a diversity of information about post-marketing risk management activities that sponsors have included in marketing applications in response to new expectations derived from the FDA PDUFA 3 performance goals. We agree with the Agency's emphasis on those few instances when, due to a serious issue, a RiskMAP is warranted. However, we believe that the Agency's expectations pertinent to the majority of marketing applications, which do not require a proposed RiskMAP, should also be addressed. We also note that the PDUFA 3 performance goals did not expand FDA's authority with regard to RiskMAPs.

While PhRMA supports most of the concepts outlined in the draft guidance documents, we are concerned that there could be a negative impact on the development of new and innovative medicines as an unintended consequence if certain concepts are applied in an inappropriate manner. Examples of such unintended consequences include requirements for pre-approval large simple safety studies that delay availability of new drug products, and RiskMAP programs that unintentionally prevent patient access to beneficial products. Indeed, burdensome RiskMAP requirements could steer patients to older products with a less favorable benefit/risk profile than one with a RiskMAP. It is critical that the FDA establishes clear transparency and consistency in the selection of products and circumstances for which additional risk assessment and risk minimization activities are requested, to ensure that patient access to new effective therapy is not jeopardized. We note that FDA's recently issued position paper "Innovation or Stagnation - Challenge and Opportunity on the Critical Path to New Medical Products" (March 2004) highlights the increase in complexity and inefficiency of the clinical development process as a major challenge for making new medicinal products available to the public. Industry and the Agency need to work together to ensure that these risk management initiatives do not add to that complexity and inefficiency.

Comments that are specific to the Draft Guidance for Industry on Development and Use of Risk Minimization Action Plans are attached. These are being submitted in two parts: (1) a memorandum outlining PhRMA's position regarding the limitations on FDA's authority to impose RiskMAP requirements; and (2) a memorandum providing line-by-line comments on the RiskMAP draft guidance. Our comments on the other two draft guidance documents are submitted separately to the respective dockets.

We thank FDA for the opportunity to comment on this important topic. Please do not hesitate to contact me if any of the issues presented herein require clarification. PhRMA member companies look forward to continued dialog as the Agency proceeds with this significant initiative.

Sincerely,

PhRMA Comments on FDA Draft Guidance for Industry: Development and Use of Risk Minimization Action Plans
Docket No. 2004D-0188

June 28, 2004

General Comments:

The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased that the Food and Drug Administration (FDA) has significantly reflected in the draft Guidance the public input it received on the corresponding concept paper, and that the Introduction and Background sections of the document have been coordinated with the two companion draft guidance documents. PhRMA is in agreement with FDA's proposal to drop the term "Risk Management Program" in favor of Risk Management Action Plan (RiskMAP) for purposes of clarity.

PhRMA also believes that the following enhancements included in the draft guidance represent substantial improvements:

- The focus of the draft guidance is on evidence based decision-making.
- It reflects the need to build on previous experience with respect to the selection of risk tools.
- For most products routine risk minimization efforts will be sufficient; few products are likely to warrant RiskMAPS.
- Safety enhancement is appropriately balanced with patient access; RiskMAPS should be used judiciously to minimize risks without interfering with delivery of benefits to patients or overburdening the healthcare system.
- It reflects the spirit of maintaining a dialog and information exchange between FDA and the sponsor, while protecting proprietary aspects arising from these interactions.
- FDA has eliminated the four proposed Risk Management Program levels.
- The Agency acknowledges health practitioners as the most important managers of product risks.

PhRMA member companies are pleased to see that the FDA makes it very clear in the proposed guidance that for most products, routine risk minimization measures are sufficient, and that only a few products are expected to have risks warranting a RiskMAP. We agree that for most products appropriate product labeling along with good post-marketing surveillance is sufficient. Since this is a primary tenet of the proposed guidance documents, we believe this concept should be reinforced at the Office level by monitoring the number of products that require RiskMAPs and providing annual statistics to industry.

Although the guidance document provides considerable information regarding when a RiskMAP should be considered, it also includes a statement that the FDA may recommend that a sponsor consider a RiskMAP based on the "Agency's own interpretation of risk information." This approach is of concern in that consistent standards must be used across all review divisions so that individual reviewers don't use different criteria in requesting such plans. PhRMA believes this is important in order to provide an evidence-based rationale for RiskMAPs for every drug for which they will be requested. There must be sufficient oversight to ensure that decisions to request additional studies or a RiskMAP and the selection of tools to be employed are made consistently between Centers and across review divisions. This includes consistency with regard to RiskMAP requirements for generic products. PhRMA requests that FDA describe its plans to monitor consistency across the Agency, to ensure that products in the same/similar class with similar safety profiles meet risk minimization expectations in a uniform matter. Furthermore, it should be made clear in the guidance document that patient access to newer products should not be jeopardized by the existence of a RiskMAP.

In our comments on the draft concept paper, PhRMA suggested that FDA include a complete review of all current and past RMPs, to demonstrate the value of these overall programs as well as the individual tools used to achieve the objectives. PhRMA appreciates that the FDA is proposing to maintain a RiskMAP Web site, but it appears that the information will be primarily comprised of the data that FDA receives from sponsors and others. PhRMA member companies would like to see an analysis by the FDA of previous plans and the tools used, including overall feasibility assessments, as well as the known advantages, disadvantages, and limitations associated with a given tool. Other tools, which have not yet been shown to be effective or which have not been validated should be described as potential or as "results pending". We understand there could be confidentiality issues, but believe that such an analysis could be done and still retain appropriate confidentiality since a number of programs have been publicly discussed. The web site could also provide annual statistics regarding the number of products requiring a RiskMAP.

Although the draft guidance document stresses that RiskMAPs will only be required for serious issues and should be quite rare, it has become somewhat unclear whether a voluntary activity would be considered an element of a RiskMAP. As reflected by industry's previous concerns about the levels proposed in the corresponding concept paper, it can be expected that any drug with a RiskMAP will be perceived as "riskier" than those without one (i.e., the so called "risk management irony"). PhRMA notes that many of the items listed as tools for targeted education and outreach have other uses besides risk minimization, but even when deployed for other uses may contain information on the safety of a product. PhRMA also notes that many products employ these types of tools for routine risk management. By defining these as elements of formal RiskMAPs, FDA undercuts its assertion that RiskMAPs should apply only to a select few products. PhRMA thus requests that FDA clarify that these targeted education and outreach tools are considered to be routine, voluntary risk management tools, not formal RiskMAP tools that are covered by the guidance.

During public presentations regarding the Risk Management concept papers, FDA representatives have noted that sponsors have included a diversity of information about post-marketing risk management activities in marketing applications (i.e., level of detail, format used). PhRMA agrees with the Agency's emphasis on what should be submitted to FDA in those instances when a RiskMAP is needed that affects the marketing application (e.g., change in labeling). However, unless the RiskMAP affects the approved conditions of use, we do not believe it should be submitted to FDA as part of the marketing application or in a supplement. Such information can be communicated to FDA in an informal submission. We would welcome additional information pertinent to the content/format issues related to risk management information that should be submitted for the majority of drugs that do not warrant a RiskMAP or do not warrant a change to the marketing application.

PhRMA believes it is critical for FDA to discuss in the guidance the circumstances and mechanisms by which it would be appropriate for a sponsor to scale back or discontinue elements of a RiskMAP (e.g., goal achieved, prescribing habits established, etc.). We do not believe that a sponsor must expect that once established, a RiskMAP will always have to be a component of the product's conditions of marketing. We request that FDA address this as part of the guidance.

In addition, PhRMA suggests that FDA describe how this guidance relates to the suggested submissions described in the ICH E2E draft Guidance on Pharmacovigilance Planning. We believe that a global approach to pharmacovigilance and risk management is very important, and we strongly urge FDA to harmonize with international consensus initiatives.

Specific Comments

Section: II.B. Overview of the Risk Management Draft Guidance Documents

Line(s)	Comment
58-59	PhRMA suggests that the sentence be revised to read: "(2) developing and implementing tools to minimize its risks while preserving or enhancing benefits to all or a subset of the target population."
63	PhRMA suggests that the following sentences be added to the end of this paragraph: "FDA explicitly recognizes that depending on personal preferences, disease, stage of disease and aggressiveness of the progression of the disease, some persons may wish to trade more risk for benefit. RiskMaps can be used to enable that tradeoff by recognizing those preferences."
76-77	With regard to the statement that the recommendations in this guidance focus on situations when a product may pose an unusual type or level of risk, we suggest that FDA clarify that the guidance applies only to those established risks, and not to hypothetical risks. For example, the recommendations should not be applicable for a product with limited safety information at the time of approval (i.e., it is unknown whether this product may pose an unusual level of risk). We also suggest that this sentence be revised to read: "... when a product may pose an unusual type or level of risk to all or a subset of the target population."
88-89	Reference is made to international harmonization efforts. PhRMA notes that the draft ICH E2E guidance, which has also recently circulated for public comment, includes proposals for submission of Pharmacovigilance Specifications and Pharmacovigilance Plans. We suggest that the draft guidance for RiskMAPs and the draft Guidance for Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment reflect how these FDA guidance documents correlate with the ICH E2E guidance.

Section: III. The Role of Risk Minimization and RiskMAPs in Risk Management

Line(s)	Comment
	Since section C introduces the concept of a Risk Management Action Plan (RiskMAP), we suggest that this information precede the information presented in section B.
108	PhRMA suggests that the first sentence in this paragraph be changed to: "...risk assessment, risk minimization, and/or benefit enhancement."
112-113	PhRMA suggests that this sentence be changed to: "...while preserving or enhancing its benefits to all or a subset of the target population."

Section: III.A. Relationship Between a Product's Benefits and Risks

Line(s)	Comment
128-138	Discussion of the benefit-risk tradeoff appears very heavily weighted toward the "population" at risk and insufficiently targeted to the individual. The issue is more than simply a minimization of risks for the fixed benefits of the population at risk; many sub-groups and individuals would be willing to accept (trade off) more risk for benefit depending on personal preferences, disease, stage of disease and aggressiveness of the progression of the disease. That FDA recognizes this is somewhat intimated in lines 128-138 and lines 409-421; it bears repeating and stating explicitly throughout, though. Risk assessments and plans should enable the FDA to permit targeted indications to individuals for use of a treatment where risk is higher than that for the total population at risk, thereby enabling patients and their physicians to make more appropriate treatment choices. This is more than just minimization of risks for a given benefit; this is acknowledgment of individual preferences and rights for a trade-off. We suggest that a statement to this effect be added to the guidance document.
132-133	With regard to the statement that risks and benefits are usually measured in different

	units, it should be mentioned that a number of methods that put benefits and risks of a drug product in the same context are under development (see additional comments related to lines 212-217).

Section: III.B. Determining an Appropriate Risk Minimization Approach

Line(s)	Comment
143-150	The draft guidance directs major efforts towards continuous risk ascertainment, minimization and evaluation of a small number of therapeutic safety issues, since as noted in lines 150-151, for most products, routine risk management will be sufficient and a RiskMAP need not be considered. We appreciate the efforts to provide clear guidance on RiskMAPs, however, this provides little guidance for FDA approved professional labeling, the method that FDA "considers the cornerstone of risk management efforts for prescription drugs", and which is the risk minimization tool for most therapeutic agents. This is particularly important since this aspect is not specifically covered in the Pharmacovigilance and Pharmacoepidemiology Guidance either. It is impossible to provide guidance on every possible scenario and situation. However, a first step in raising awareness of this situation would be to modify the paragraph in lines 142-150. We suggest that the middle section of this paragraph be revised to read: "... updated from time to time to incorporate information from post-marketing surveillance or clinical and epidemiology studies (including patient characterization and therapeutic utilization studies) revealing new benefits (e.g., new indications or formulations), risk concerns, or adherence to label recommendations. It is in the interest of patients, sponsors, and FDA to further our knowledge about the effectiveness of labeling as a risk management tool. Efforts to make..."
151	If the order of sections B and C are not switched, the first use of the term RiskMAP should be defined.
158	PhRMA suggests this statement be relocated to follow the text on line 165 (see comment above regarding switching the order of sections B and C).

Section: III.C. Definition of Risk Minimization Action Plans (RiskMAP)

Line(s)	Comment
163	This sentence should be changed to read: "...while preserving or enhancing its benefit."
168-171	PhRMA suggests the following wording: "FDA suggests that sponsors state goals in a way that aims to achieve maximum risk reduction within the context of, and accounting for, the individual life situations of the target patient population." Also, "FDA recommends that goals be stated in absolute terms, where possible, allowing for discretion by doctors and patients according to physician judgment and individual preferences for risk."
171-173	PhRMA suggests that FDA change the last sentence of the paragraph to read: "Although it might not be possible to ensure that absolutely no one on X drug receives Y drug, FDA believes that a *goal,* as the term implies, is a vision statement of the ideal outcome of the RiskMAP."
179-181	PhRMA is concerned that the proposed objectives may blur the line between the role of pharmaceutical companies and the role of health care providers. While we support the role of pharmaceutical companies in attempting to minimize risk to patients as much as possible through communication and possibly other efforts, PhRMA does not believe it is the companies' responsibility to "police" health care providers.

Section: III.D. Determining When a RiskMAP Should be Considered

Line(s)	Comment
193-228	PhRMA believes this section is unduly vague and overly broad. As currently written, virtually any product on the market could be determined to need a RiskMAP of one form or another to "improve the product's benefit-risk balance." This is contrary to FDA's stated intent throughout the draft Guidance that routine risk minimization measures (e.g., labeling) are sufficient for the vast majority of products and that only a few products are likely to merit consideration for additional risk minimization efforts. We thus suggest that FDA re-write this section to: (1) reiterate that a RiskMAP should be considered for only a limited number of products; and (2) define more specifically, based upon existing examples, when a RiskMAP should be considered. For instance, we do not believe a RiskMAP should be considered whenever it might "improve" the product's benefit-risk balance, since any approved product should already have a positive benefit-risk balance. Rather, a RiskMAP may be needed where the risks otherwise would outweigh the benefits for the entire patient population or a particular subset of the population. In the event FDA declines to re-write this section as suggested, the following comments are provided on the existing text.
193	It is important to recognize the value of early dialog between Agency and the sponsor, which should be before a decision to implement Risk MAP is made. A reminder to that effect should be inserted as a prefatory statement to Section D.
193 (foot-note 6)	This note mentions that a generic product "...**may** have the same or similar benefit-risk balance as the innovator..." (emphasis added). PhRMA questions use of the word "may," since generic products, by definition, should have an identical benefit-risk balance as the innovator. This is the very basis for their approval without a full data set. We request thus request that FDA modify this statement accordingly.
195-201	The draft guidance avoids specific descriptions of the nature of adverse events that may warrant a RiskMAP. In addition to the information presented on lines 206 to 228, we suggest that this section reflect that consideration of a RiskMAP requires certain activities that can reasonably be expected to result in appropriate product use and that if the desired behaviors of prescribers, other HCPs, or patients can be assured, the overall benefit-risk balance can be enhanced. This means that an acceptable benefit-risk balance depends on the following attributes: • the risks are in some way preventable, • a sub-population that may receive greater benefits of the drug can be identified (e.g. identifying who is most likely to benefit via assessment of a biomarker), or • given the potential severity of a possible rare risk, informed decision making by patients and prescribers must be assured.
212-217	The document suggests that "nature and rate of known risks versus benefits" be considered when trying to determine if development of a RiskMAP is desirable. The need to compare benefits to risks is obvious, although we agree with the FDA that such an assessment is a very complicated process. To minimize bias in how the risks are weighted in light of benefits, it might be useful for the FDA to consider models as they make such assessments in the future. Currently, this benefit-risk assessment is basically a judgment call, and that is partially due to the fact that most models are not sophisticated enough to be useful or have not been validated. While that is still the case, more work is being done with respect to evaluating such models. Exploring the use of models such as these might be considered as a way to help bring consistent thinking into the FDA review process concerning the balance of benefits and risks for drug products throughout their life cycle. A more rigorous approach may help to ensure that the assessment is not influenced, for example, by placing an inordinate emphasis on a very rare risk or on merely theoretical risks, and that the assessment is actually more balanced.

	PhRMA also suggests that "preferences of the population at risk for both benefits and risk in the context of their medical situation" be added as a fifth characteristic to be weighed (line 217).
224	PhRMA suggests adding a bullet point specifying that a generic product should have the same RiskMap as the innovator product. We question why a generic product would not automatically have the same requirement for a RiskMAP as the innovator product, since they would have the same benefit/risk profile.
225-228	This section appears to be an obvious reference to the case represented by the Oxycontin experience. However, it seems arbitrary and out of place that a specific category such as Schedule II controlled substances have been singled out as examples of when a RiskMAP should *always* be considered. We suggest this section be deleted or simplified as an additional bullet: "there is significant risk-associated abuse and product diversion."

Section: IV. Tools for Achieving RiskMAP Goals and Objectives

Line(s)	Comment
230	When discussing various tools for risk management it is important to keep in mind that there may be an opportunity to learn and share various experiences. PhRMA applauds the Agency's plans to make tools available and transparent, to a certain level. These may serve as learning opportunities and help various companies to avoid mistakes and apply successfully new learning.

Section: IV.B. Categories of RiskMAP Tools

Line(s)	Comment
258-343	The previous concept paper on this topic called for categorizing RMPs into levels. We were not in favor of this for many reasons and we are happy to see that the FDA has rethought this position. Instead there is a description of categories of RiskMAP tools, which seems to be a more appropriate approach. We were also pleased to see that the proposed guidance notes that a selection of specific tools should not be used in an assessment of comparative safety to another drug product.
267-297	PhRMA suggests either deleting section IV.B.1 regarding "Targeted Education and Outreach" tools or clarifying that these tools are not considered to be formal RiskMAP tools subject to the guidance. This revision is necessary to ensure that RiskMAPs (and the RiskMAP guidance) apply only to a select few products as intended by FDA. Many products on the market – certainly more than a select few -- utilize these types of targeted education and outreach tools as part of their routine risk management activities (and for other purposes). PhRMA thus believes that these should not be viewed as formal RiskMAP tools subject to this guidance but rather as routine risk management tools on par with labeling and post-market surveillance. Otherwise, the universe of products subject to RiskMAPs will balloon well beyond the select few contemplated by FDA and industry, contrary to the intent of the guideline.
281	PhRMA requests that FDA delete this bullet point since it suggests that pharmaceutical companies can and should control the content of Continuing Medical Education (CME) activities for healthcare practitioners. These programs typically are independent of company influence or control and thus should not be considered a RiskMAP tool that can be employed by a pharmaceutical company.
286	PhRMA suggests addition of another bullet at the top of the page: "disease management programs, such as patient-provider interaction systems"
310-311	From a liability perspective, it is problematic for manufacturers to certify practitioners. We suggest that successfully completing Continuing Education may meet this

	objective. PhRMA also requests clarification regarding the distinction between a certification program for practitioners (as a reminder system) and training programs for health care practitioners (as targeted education and outreach).
313	Similarly, we request clarification regarding the distinction between special educational programs that reinforce appropriate product use (as a reminder system) and training programs for health care practitioners and patients or continuing education for health care practitioners (as targeted education and outreach).
320-321	The last bullet, "specialized systems or records that attest to safety measures having been satisfied (e.g., prescription stickers, physician attestation of capabilities)" appears to belong in the third category, Performance-linked Access Systems.
323-343	Performance linked access systems should not be burdensome for prescribers or sponsors. If not carefully planned they may have an opposite effect.
332-343	PhRMA suggests that the guidance also reflect the use of distribution or use restrictions under 21 CFR 314 Subpart H (Accelerated Approval of New Drugs for Serious or Life-threatening Illnesses).

Section: IV.C Description of RiskMAP Tools

Line(s)	Comment
345-354	PhRMA is supportive of a FDA web site that summarizes contemporary experience with risk tools consistent with federal laws and regulations governing disclosure of information to the public. However, as mentioned in our general comments above, we believe that the web site should also contain FDA's analyses of previous plans and the tools used, including overall feasibility assessments, as well as the known advantages, disadvantages, and limitations associated with a given tool.

Section: IV.D. Selecting and Developing the Best Tools

Line(s)	Comment
372-374	PhRMA is particularly pleased with the emphasis on the need to balance measures to enhance safety with patient access.
386-387	PhRMA suggests that this bullet be moved to follow the first bullet.
391	PhRMA suggests that this statement be revised to read: "compatible with current technology that is widely available".
406-407	The proposed guidance states that the design of the RiskMAP should seek to avoid unintended consequences of tool implementation that obstruct risk minimization and product benefit. PhRMA absolutely agrees with the point, but we would like to see more information from the FDA regarding how they propose to ensure that this does not occur. One of the most obvious ways that this occurs is when an inappropriately onerous RiskMAP drives doctors and patients to use a riskier drug that does not have a RiskMAP. As stated above, this scenario has not been adequately addressed in the proposed guidance.
409-421	PhRMA recommends that FDA add text to reflect that like FDA, pharmaceutical manufacturers cannot control the actions of prescribers, and should not interfere with medical or surgical practice. However, tools applied as part of RiskMAPS are intended to facilitate safe use of the product in accord with its labelling. PhRMA also recommends that FDA consider modifying this statement to indicate that health care practitioners are "...one of the most important managers of product risk", since for some products and events, patients may be the primary target for risk

	communication. Consider moving this section to section IV.A. (following line 256).

Section: V.A. Rationale for RiskMAP Evaluation

Line(s)	Comment
453 (foot-note 9)	The author of the Clin Pharmacol Ther paper is BL Strom (not Nordstrom).
469-471	There is an apparent contradiction between the statement in lines 469-471 ("Statistical hypothesis testing would not typically be expected, given the limitations of the data likely to be available") and a later statement in lines 817-819 ("measurement errors, sensitivity, specificity, as well as power and confidence intervals where appropriate"). This later statement implies that the data will have more rigor than is generally expected. We request that FDA clarify this seeming contradiction.

Section: V.B. Considerations in Designing a RiskMAP Evaluation Plan

Line(s)	Comment
476-477	RiskMAP evaluation plans are "...designed to assess whether the RiskMAP's goals have been achieved through its objectives and tools." However, most goals will not be 100% achievable because of human fallibility and the FDA's acknowledged lack of jurisdiction over physician's prescribing or medical practice. This limitation should be acknowledged or described in the guidance document.
482-508	RiskMAPs should seek continuous improvement until an acceptable risk-benefit balance is maintained. Specific quantitative reporting goals are particularly problematic as are *a priori* thresholds for action. Refinements of a RiskMAP require an assessment of the quantity and quality of reports, nature and severity of events that occur after the interventions have had time to make an impact. The decision to add, modify or remove tools requires a comprehensive assessment of all available information rather than focus on an isolated metric.
486-488	If the final guidance retains the requirement for specific quantitative goals, it is imperative that the agency provide guidance on the criteria to be used for goal setting. A specified number or rate of a complication may not be established at time of initiation of RiskMAP. For example, if a drug is the first in the class and/or the background rate of the adverse event of interest has not been studied, especially within the RiskMAP environment, it would be difficult to define the threshold.
488	PhRMA suggests that this sentence be changed to: "...than a specified number or rate of that complication, or improving the outcome of the adverse event."
488-508	The draft guidance document states that if health outcomes cannot be practically or accurately measured, closely related measures can be used. PhRMA questions how often health outcomes can be practically or accurately measured and at what cost. We request that FDA acknowledge that it might take a significant time for enough data to become available to prove that rates of an event have gone down and by how much. PhRMA requests additional discussion on the decision-making process for selecting to monitor an actual patient outcome versus a closely related measure. On line 493, we suggest that "pregnancy tests for pregnancy status" be deleted as an example of a surrogate health outcome measure, as pregnancy tests are often used to rule out pregnancy, not only to confirm it. On line 505, FDA refers to "complete ascertainment of pregnancies" as an example of a validity measure. We suggest the word "complete" be deleted since 100% ascertainment is an unrealizable real-world objective.

516-518	Spontaneous AE data are described as "potentially" biased outcome measures. We suggest that this be corrected to say that spontaneous report data are "inherently biased outcome measures..."
522-530	This section appears to suggest that claims databases do not include patients of lower socioeconomic status. However, Medicaid claims databases have data on medical care to some categories of economically disadvantaged and disabled persons. In addition, because of the infrastructure of the European health care system, many European pharmacoepidemiologic databases include a sample of all patient groups, irrespective of socioeconomic status.
568-571	The proposed guidance discusses the potential for an evaluation of a RiskMAP to allow the opportunity to discontinue a tool if the individual tool is performing poorly. While poorly performing tools should be discontinued, we would also like to see the acknowledgement that it might be appropriate to discontinue a tool if it proved to be successful and therefore was no longer needed, or if there were another redundant tool which superceded the need for the tool.
590	PhRMA requests clarification regarding the tools for which sponsors would be expected to perform pre-testing in a clinical trial setting such as a large simple safety study. Including testing of tools in clinical trials would add a layer of complexity to both the performance and analysis of the trials and could possibly lead to an increase in sample size to assure adequate population of analytical cells.

Section: V.C. FDA Assessment of RiskMAP Evaluation Results

Line(s)	Comment
611-613	PhRMA recommends that FDA commit to share the results of its assessment of the RiskMAP effectiveness with the sponsor/applicant and discuss any differences of interpretation (reference line 652).

Section: VI. Communicating with FDA Regarding RiskMAP Development and Design Issues

Line(s)	Comment
645-646	To initiate a dialog with FDA regarding the Agency's experience with previously implemented RiskMAPs, it would seem logical for a sponsor/applicant to also be able to contact the Office of Drug Safety, as they would have experience with a broader range of products and RiskMAPs than a single review division. We suggest revising the end of this sentence to read: "...contact the product's review division for product-specific risk management issues, or the Office of Drug Safety for information on FDA's general experience with risk management tools".
666-668	Please clarify whether a pre-approval RiskMAP should be submitted to both the IND and the pending NDA/BLA, or to only one of these files.
669-670	FDA recommends that RiskMAPS proposed post-marketing should be submitted as a supplement to the NDA or BLA. Unless the RiskMAP is proposing a change to the approved conditions of use of the product (e.g., labeling change), we do not believe it is appropriate to submit RiskMAP information as a formal supplement. For those instances where a supplement is appropriate, the guidance document should specify how or if user fees will apply to submission of these supplemental applications.

Section: VII.A. Contents of a RiskMAP Submission to FDA

Line(s)	Comment
679	In this section, PhRMA agrees with the Agency's emphasis on what should be submitted to FDA in those instances when a RiskMAP is needed. However, as noted in our general comments above, we feel that the Agency should also address its expectations pertinent to the content/format issues related to risk management

	information to be included in marketing applications for the majority of drugs that do not warrant a RiskMAP.
728-730	It is unclear what success or failure experiences should be discussed here (e.g., for the specific product under discussion or for all RiskMap experience).
747-751	PhRMA requests clarification regarding the type of evidence that should be provided. There are very few examples in the public literature of successes for any tools, and most, if not all, information has already been included in the guidance document. If the tools are recommended in the guidance, what other evidence needs to be provided?
770-773	This bullet should add language to clarify that RiskMAP modification can be in either direction; new tools can be added, but tools can also be removed, or the RiskMAP terminated altogether.
779	PhRMA recommends that the Agency reconsider expecting milestones and written progress reports for all RiskMAPs. Instead, constructive dialog and information exchange between FDA and the sponsor should be based on the circumstances of the particular product.
783-784	If the requirement for written progress reports is retained in the final guidance document, we suggest that the sentence be changed to read: "FDA recommends progress reports be included in the Periodic Safety Reports (PSURs) or traditional Periodic Reports, or submitted at the same time as the sponsor submits these reports."

Section: VII.B. Contents of a RiskMAP Progress Report

Line(s)	Comment
817-818	PhRMA requests that FDA clarify what measurement errors, sensitivity, etc. are being referred to in this paragraph.
838-839	The proposed guidance states that a sponsor might choose to propose modifications to the RiskMAP "if the RiskMAP goals were not achieved". As indicated in our comments regarding lines 770-773, we believe that modifications to RiskMAPS can and should occur in both directions. We would like to see some discussion about when it might be possible to modify a RiskMAP if the goals WERE achieved. In other words, will a RiskMAP be a never-ending activity or will there be the potential for modification based on success?

July 6, 2004

VIA HAND DELIVERY

Dockets Management Branch
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: FDA Draft Guidances on Risk Management: "Premarketing Risk Assessment"; "Development and Use of Risk Minimization Action Plans"; "Good Pharmacovigilence Practices and Pharmacoepidemiologic Assessment"

Ladies and Gentlemen:

The Pharmaceutical Research and Manufacturers of America (PhRMA) submits these comments in response to the Food and Drug Administration's (FDA's) request for comments on the above-captioned draft guidances on risk management (the "Risk Management Draft Guidances"). These guidance documents were prepared by the PDUFA III Pharmacovigilance Working Group in response to the PDUFA III performance goal to produce guidance for industry on risk management activities for drug and biological products. The Risk Management Draft Guidances were prepared, in part, from comments the Agency received during a public workshop on risk management held from April 9 to April 11, 2003.

PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, healthier, and more productive lives. Investing over $30 billion this year in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures. PhRMA's members are the source of nearly all new drugs that are discovered, made, and used

worldwide. PhRMA therefore has a vital interest in the issues presented by the Risk Management Draft Guidances.

PhRMA and all of its members are committed to the safety of their products. As such, PhRMA fully supports the development of risk minimization strategies and other methods of assuring product safety where necessary. PhRMA member companies currently do this by rigorously testing their products to demonstrate safety and effectiveness prior to marketing; ensuring that products are adequately labeled with all applicable risk information; conducting comprehensive post-marketing surveillance activities to detect emerging safety issues; and, when necessary, taking appropriate action to ensure patient safety when risks are detected after marketing, such as issuing healthcare practitioner letter, updating labeling, and conducting targeted voluntary recalls. In most cases, as FDA has acknowledged, risk can be effectively minimized through these routine measures currently used by manufacturers. In rare cases, it may be beneficial for FDA and a drug's manufacturer to work together to develop a more comprehensive risk management program that incorporates more rigorous means of risk minimization.

PhRMA is submitting these comments, however, to make clear that in those cases where more than routine risk management might be desirable, implementation of a rigorous risk management program must be a collaborative process based on measures voluntarily undertaken by drug manufacturers in cooperation with the Agency. FDA does not have authority under the Federal Food, Drug, and Cosmetic Act (the "FD&C Act") to require manufacturers to implement restrictive risk management programs involving the tools discussed in the Risk Management Draft Guidances.

FDA's authority under the FD&C Act is limited to ensuring that new drugs are safe and effective so long as physicians follow the conditions of use prescribed, recommended, and suggested in the drug's labeling. These conditions of use may include such items as limited indications for use, contraindications, warnings, and suggestions to physicians (such as a recommendation that the drug be prescribed only to certain types of patients or by physicians with access to certain medical equipment). Under the FD&C Act, however, once this labeling is in place, and assuming that the drug is effective, FDA must approve the new drug.[1]

Once these conditions for use are established, it is for physicians to decide, in the practice of medicine and taking into consideration the information contained in the approved labeling, how, to whom, and under what conditions and circumstances to prescribe that drug. FDA does not have the authority to require that physicians follow the approved conditions of use. Nor may the Agency refuse to approve a new drug on the basis of the possibility that physicians may not do so. This is the essence of FDA's longstanding policy against regulation of the practice of medicine, which has been confirmed by the courts and by Congress. As a result, FDA may not attempt to ensure physician compliance with the conditions of use in the labeling by requiring that drug manufacturers implement risk management programs, particularly those involving restrictions on distribution. To do so would exceed the Agency's authority under the FD&C Act, violate FDA's longstanding policy regarding the practice of medicine, and conflict with important public policy goals.

Furthermore, there are limitations on the kinds of "conditions of use" that FDA can place in the approved labeling. Distinction must be made between labeling intended to

---

[1] *See* 21 U.S.C. § 355(d).

provide physicians with the information they need to make informed medical decisions, and labeling that is intended merely to enforce physician compliance with the approved conditions of use. Once again, this latter type of labeling exceeds FDA's authority under the FD&C Act, interferes with the practice of medicine, and conflicts with important public policy goals.

Through these comments, PhRMA does not mean to imply that FDA can do nothing to increase patient safety. PhRMA suggests only that, although the Agency's powers are broad, they are not so broad as to permit FDA to impose mandatory risk management plans. Congress provided the Agency with a limited role, in part because there are other mechanisms in place that amply serve the same purpose. Congress has given to FDA the first role in guarding patient safety by requiring that physicians may prescribe only those prescription drugs approved by the Agency. Where FDA's role ends, the role of physicians begins; patient safety is protected by the training, experience, and judgment of physicians as well as their intimate knowledge of their patients. Physicians and their practices are in turn subject to oversight by medical review boards and other certification bodies. The decisions that doctors make also ultimately may be judged by the tort law system.

PhRMA's members are committed to patient safety. They will continue to actively protect patient safety through testing, labeling surveillance, and communication activities. They also will work diligently with FDA, as they have in the past, to develop and implement voluntary risk management programs where such programs will meaningfully contribute to patient health. FDA has an important role to play in ensuring patient safety, but not the only one. Congress recognized this in drafting the FD&C Act, and limited FDA's authority accordingly.

I. The Risk Management Draft Guidances

Each of FDA's three recently published Risk Management Draft Guidances discusses a separate element of risk management. The first draft guidance document, titled "Premarketing Risk Assessment," provides FDA's views regarding how a manufacturer should structure clinical trials in order maximize the potential to recognize and identify potential significant side effects and other safety hazards posed by a given drug. The second draft guidance document, titled "Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment," covers the identification and interpretation of safety signals, pharmacoepidemiologic assessment, and the development of pharmacovigilance plans related to drug and biologic products. Although PhRMA believes that both of these draft guidance documents raise important issues worthy of serious consideration, these comments focus primarily on the legal issues raised by the third draft guidance document. PhRMA is also submitting line-by-line comments on the third draft guidance document.

The third guidance document, titled "Development and Use of Risk Minimization Action Plans," discusses design, implementation and evaluation of risk minimization action plans ("RiskMAPs"). A principal element of any RiskMAP, according to the draft guidance, is the use of one or more "tools." These tools are separated into three categories: (1) targeted education and outreach, (2) reminder systems, and (3) performance-linked access systems. Examples of targeted education and outreach tools include health care practitioner letters, training programs for health care practitioners or patients, and patient medication guides and package inserts. Examples of reminder system tools include patient agreement or acknowledgement forms, certification programs for practitioners, limiting the amount of a product in any single prescription, and "specialized systems or records that attest to safety

measures having been satisfied."[2] Examples of performance-linked access system tools include the sponsor's use of compulsory reminder systems, and restricting distribution of the product only to certain physicians (e.g., physicians with specified training or access to specified emergency medical equipment). The draft guidance urges drug manufacturers voluntarily to develop RiskMAPs using these tools in order to minimize potential hazards associated with the marketing of approved prescription pharmaceuticals.

In those rare circumstances where more rigorous risk management programs may be beneficial, FDA must recognize the limitations that Congress has placed on its authority. The development of RiskMAPs and the use of the kinds of tools described in the Risk Management Draft Guidances must be voluntarily developed and adopted by prescription drug companies. They may not be required by FDA.

II. FDA Has Limited Authority Under the FD&C Act to Approve or Deny an NDA

FDA, Congress, and the courts have long recognized that FDA should not regulate the practice of medicine. As a result, Congress specifically limited the criteria the Agency may use in making decisions to approve or deny NDAs. Recognizing these limitations, the courts have held that FDA may not impose risk management tools such as restrictions on distribution of approved drugs.

A. The Plain Language of the FD&C Act Limits the Grounds Upon Which FDA May Deny or Withdraw an NDA

Section 505(d) of the FD&C Act clearly defines the grounds on which FDA may deny an NDA. Under that section, the Commissioner *must* approve an NDA unless one of seven specifically enumerated conditions exist:

---

[2] Food and Drug Administration, Draft Guidance for Industry: *Development and Use of Risk Minimization Action Plans*, at 8 (May 2004) (RiskMAP Draft Guidance).

1. "investigations, reports of which are required to be submitted to the Secretary . . . do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use *under the conditions prescribed, recommended, or suggested in the proposed labeling thereof*";

2. "the results of such tests show that such drug is unsafe for use *under such conditions* or do not show that such drug is safe for use *under such conditions*";

3. "the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity";

4. "upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use *under such conditions*";

5. "evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof";

6. the application failed to contain required patent information; or

7. "based on a fair evaluation of all material facts, such labeling is false or misleading in any particular."[3]

The provision specifically states that if FDA finds that none of these clauses apply, FDA "*shall* issue an order approving the application."[4] Thus, Congress has made clear that FDA may deny an NDA only if one of these seven enumerated conditions exists.

Similarly, Section 505(e) of the FD&C Act sets forth the conditions under which FDA may withdraw the approval of an NDA. With regards to safety, FDA may withdraw approval of an NDA only if it finds that one of the following specifically enumerated conditions exist:

---

[3] 21 U.S.C. § 355(d) (emphasis added).

[4] *Id.*

1. "clinical or other experience, tests, or other scientific data show that such drug is unsafe for use *under the conditions of use upon the basis of which the application was approved*"; or

2. "new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use *under the conditions of use upon the basis of which the application was approved.*"[5]

Once again, FDA may withdraw approval of an NDA (for safety reasons) only if it legitimately finds that the drug is not safe *under the conditions prescribed, recommended, or suggested in the proposed labeling* (i.e. the "conditions of use upon the basis of which the application was approved").

The common feature of all of the grounds for denial or withdrawal is a finding that the drug is not safe *under the conditions prescribed, recommended, or suggested in the proposed labeling*. If a given prescription drug would be safe if used in the manner directed in the approved labeling, FDA must approve that drug. FDA may not refuse to approve a prescription drug on the ground that the drug might not be safe if a physician, pharmacist, or patient were to use the drug in a manner *other* than is prescribed, recommended, or suggested in the proposed labeling. Nor does the FD&C Act permit the FDA to approve a drug only under conditions beyond those prescribed, recommended, or suggested in the labeling. To do so would be to create an eighth ground for denial of an NDA, which Congress did not provide for in section 505(d). Congress intended, therefore, that FDA may deny or withdraw an application only if no conditions of use can be crafted in the labeling under which the drug would be safe and effective *if those conditions are followed by physicians*.

---

[5] 21 U.S.C. § 355(e).

B. The Courts Have Affirmed a Limited Interpretation of FDA's Authority

Based in large part on the limited authority that Congress granted to FDA in sections 505(d) and (e), the courts have already held that FDA has no authority to require restrictions on distribution of prescription drug products. In *American Pharm. Ass'n* v. *Weinberger*, the United States District Court for the District of Columbia considered FDA's attempt to place restrictions on a manufacturer's distribution of methadone to only certain physicians.[6] Methadone was originally approved as a safe and effective agent in the treatment of severe pain and for antitussive purposes. Eventually, however, the drug became a maintenance drug for heroin addicts. In an attempt to control abuses in the distribution of methadone, FDA issued a regulation restricting the distribution of methadone to maintenance treatment programs and hospital and community pharmacies designated by FDA and withdrew the approved NDAs covering the non-maintenance indications.[7] FDA thus effectively prohibited most licensed pharmacies from dispensing methadone, even when lawfully prescribed by a physician.

FDA argued that the risk of misuse justified restricting distribution to designated facilities. The Methadone Regulation stated that FDA was withdrawing the NDAs because of "a lack of substantial evidence that methadone is safe and effective for detoxification, analgesia, or antitussive use *under the conditions of use that presently exist.*"[8] It maintained that section

---

[6] 377 F. Supp. 824 (D.D.C. 1974) *aff'd per curium sub nom., American Pharm. Ass'n* v. *Mathews*, 530 F.2d 1054 (D.C. Cir. 1976).

[7] Food and Drug Administration, Final Rule: *Approved New Drugs Requiring continuation of Long-Term Studies, Records, and Reports, Listing of Methadone with Special Requirements for Use*, 37 Fed. Reg. 26790 (Dec. 15, 1972) (hereinafter the "Methadone Regulation").

[8] *Id.* at 26794.

505(d) of the FD&C Act authorized the Agency to withdraw approval of the NDAs on the ground that the drug could not be secured against misuse even when lawfully prescribed.[9]

The United States District Court for the District of Columbia disagreed and invalidated the Methadone Regulation. The court found that in assessing the safety of a drug under section 505(d), FDA is entitled to consider only the safety of the drug "when used in the manner intended" and could not take the risk of "misuse" into account in its approval determination.[10] In making this determination, the court reasoned that:

> FDA's discretion under the Act's NDA provisions is limited to either approving or denying NDAs and *nowhere is FDA empowered to approve an NDA upon the condition that the drug be distributed only through specified channels.*[11]

Contrary to FDA's previous suggestion, the applicability of the *Weinberger* case is not limited to drugs that are controlled substances under the Controlled Substances Act. In the preamble to FDA's proposed Subpart H regulations, FDA argued:

> Because methadone is a controlled substance within the provisions of the Controlled Substances Act, which is implemented by the Drug Enforcement Administration with[in] the Justice Department, the district court concluded that the question of permissible distribution of the drug was within the jurisdiction of the Justice Department, not FDA.[12]

The plain language of the *Weinberger* opinion demonstrates, however, that the court's reasoning applies to all drugs approved under the NDA provisions of the FD&C Act, not only to controlled substances. The district court rested its decision on the plain language of the FD&C Act, which,

---

[9] *See id.*

[10] 377 F. Supp. at 828-30.

[11] *Id.* at 828 n.9 (emphasis added).

[12] Food and Drug Administration, Final Rule: *New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval*, 57 Fed. Reg. 58942, 58951 (April 15, 1992).

the court pointed out, "nowhere" empowers FDA "to approve an NDA upon the condition that the drug be distributed only through specified channels."[13] In support of this broad conclusion, the court interpreted the term "safe" as used in the approval and withdrawal provisions of the FD&C Act:

> by examining the term 'safe' in the context of [the FD&C Act] in which it appears as well as in relationship to the provision of the Act which specifically deals with controls, the Court concludes that the term 'safe' was intended to refer to a determination of the inherent safety or lack thereof of the drug under consideration *when used for its intended purposes.*[14]

The court contrasted this with FDA's argument that it could deny or withdraw an NDA based on "conditions of use that presently exist" rather than conditions of use as prescribed, recommended, or suggested in the drug's label.[15] Thus the court's reasoning makes clear that FDA's decisions to approve or deny approval of an NDA must be based only on a determination of whether the drug's labeling describes conditions of use which, if followed, would permit the drug to be administered safely.[16]

Contrary to the view that FDA described in the preamble to the final Subpart H regulation, the court did not rest its decision on the status of methadone as a controlled substance. Instead, it treated the availability of distribution restrictions under the Controlled

---

[13] 377 F. Supp. at 829 n.9.

[14] *Id.* at 829 (emphasis added).

[15] *Id.* at 828.

[16] *Id.*

Substances Act as evidence that Congress did not intend to give FDA authority to restrict distribution.[17]

The United States Court of Appeals for the D.C. Circuit affirmed the district court's decision *per curium*.[18] In a concurring opinion, Judge McGowan clearly adopted the view that FDA may place recommendations or suggestions for safe use in the approved labeling, but may not require restrictions or conditions of the manufacturer:

> The word 'safe' in section 355(d) is, to my mind, best interpreted as *requiring the labeling to include the evidence from drug testing, and the inferences therefrom, indicating the therapeutic benefits, possible dangers, and uncertainties involved in use of a drug, as an aid to a conscientious physician in determining appropriate medical treatment.* That view seems to me to accord with both the most reasonable interpretation of the statutory language and the common understanding of the FDA's mission. Thus, methadone is safe for its intended use notwithstanding the possibility that it will be employed in unintended fashions . . . . There would be almost no limit to the FDA's authority were its view adopted.[19]

Judge McGowen went on to distinguish restrictions on distribution from prescription-only restrictions. He noted that it was impractical for the labeling of drugs that would otherwise be prescription-only to contain enough information to make them safe for use by lay people. "Thus, restrictions to a prescription-only basis are necessary to ensure that persons intending to use drugs in accordance with the implications of medical evidence gathered by the FDA and contained in a drug labelling (sic) can do so."[20] By contrast, Judge McGowen noted that labeling *can* contain sufficient information to enable physicians to use drugs safely. He therefore

---

[17] *Id.* at 829 (FDA authority under the FD&C Act to prohibit distribution is incompatible with the license revocation provisions of the CSA).

[18] *American Pharm. Ass'n* v. *Mathews*, 530 F.2d 1054 (D.C. Cir. 1976).

[19] *Id.* at 1055, McGowan, J., concurring (emphasis added).

[20] *Id.* at 1056.

reasoned that restrictions such as those imposed by the Methadone Regulation exceed FDA's authority under the FD&C Act.

III. Imposition of Restrictions on Distribution or Other RiskMAP Tools Is Inconsistent With FDA's Practice of Medicine Policy

Any attempt by FDA to impose RiskMAPs on prescription drug manufacturers would result in Agency interference with the practice of medicine. FDA has repeatedly stated, however, that it does not have legal authority to interfere with the practice of medicine. PhRMA is pleased that FDA has reaffirmed this position in the RiskMAP Draft Guidance, stating:

> FDA does not have authority under these provisions to control decisions made by qualified health care practitioners to prescribe products for conditions other than those described in FDA-approved professional labeling, or to otherwise regulate medical or surgical practice.[21]

The policy has also been affirmed by the courts.[22]

There are strong public policy grounds supporting the longstanding prohibition against FDA interference with the practice of medicine. For example, physicians denied access to prescription pharmaceuticals (*e.g.* through a RiskMAP tool) will be unable to exercise their medical judgment, informed by intimate knowledge of their patients, regarding when or how to use prescription drugs. FDA must and does recognize that the Agency's prescriptions, recommendations, and suggestions are only the beginning, not the end, of the best health care decisions for patients. FDA has long-recognized, for example, that off-label uses are frequently

---

[21] RiskMAP Draft Guidance at 10-11.

[22] *See, e.g.*, *Ortho Pharm. Corp.* v. *Cosprophar, Inc.*, 32 F.3d 690, 692 (2nd Cir. 1994)("FDA permits doctors to prescribe drugs for 'off-label' uses."); *Weaver* v. *Reagan*, 886 F.2d 194, 198 (8th Cir. 1989)("FDA approved indications were not intended to limit or interfere with the practice of medicine nor to preclude physicians from using their best judgment in the interest of the patient.").

medically appropriate and may in some cases advance the standard of care. In a 1982 FDA Drug Bulletin, FDA stated that:

> The FD&C Act does not . . . limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Such 'unapproved' or, more precisely, 'unlabeled' uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature . . . . [A]ccepted medical practice often includes drug use that is not reflected in approved drug labeling.[23]

Similarly, a physician's decision to prescribe a drug despite suggestions in the labeling that such physician not prescribe the drug (for example because of a lack of access to certain emergency medical equipment), may reflect sound medical judgment that FDA is simply not in a position to make. FDA lacks the one-on-one knowledge of patients and their specific health care needs that would be necessary to substitute the Agency's judgment (through mandatory risk management tools) for the physician's.

Finally, FDA interference with the practice of medicine can impede the progress of medical science. As discussed above, FDA has recognized that independent medical judgments (such as the decision to treat a medical condition with a drug that has not been approved for that treatment) sometimes expand the standard of care for certain disease states. For example, in testimony before Congress, former FDA Commissioner Michael Friedman testified that "[o]ff label uses . . . can be of great value. Some off label uses have been of great historical importance."[24] This same public policy rationale can apply to other prescribed,

---

[23] *Use of Approved Drugs for Unlabeled Indications*, 12 FDA Drug Bulletin 4, 5 (April 1982).

[24] *Off-Label Drug Use and FDA Review of Supplemental Drug Applications: Hearing Before the Subcomm. on Human Resources and Intergovernmental Relations of the Comm. on Gov. Reform*

recommended, or suggested conditions of use (such as risk management tools) in the approved labeling. Medical science, including the understanding of risks and steps needed to minimize them, evolves more quickly than an FDA approved package insert.

Were FDA to impose risk management tools such as restrictions on distribution or use, it would necessarily interfere with the practice of medicine and conflict with these public policy goals. Physicians who are denied access to drugs through the operation of mandatory risk management tools would be precluded from "making the final judgment as to which, if any, of the available drugs his patient will receive in the light of the information contained in their labeling and other adequate scientific data available to him," or "using their best judgment in the interest of the patient." Patients of such physicians would thereby be denied the benefit of the medical judgment of their chosen physicians, with FDA in effect substituting its judgment for that of the treating physician with a relationship with the patient.

IV. FDA May Make Prescriptions, Recommendations, or Suggestions to Physicians as Part of the Approved Conditions of Use But May Not Require Risk Management Programs

Congress's decision to restrict FDA's authority under the FD&C Act reflects these considerations. As stated above, FDA is charged with ensuring that all new drugs can be safely prescribed *if* physicians follow the conditions of use prescribed, recommended, and suggested in the drug's labeling. As part of these conditions of use, FDA may suggest or recommend that physicians take certain precautions before prescribing a given drug. Just as physicians are free to prescribe medications for unlabeled indications, however, physicians are similarly free to prescribe medications in ways that do not conform with these other prescribed,

---

and Oversight, 104th Cong. . 2d Sess. 61-62 (Sept. 12, 1996) (statement of Commissioner Michael Friedman).

recommended, or suggested conditions of use in the labeling. This approach is consistent with the limited authority Congress granted FDA in the FD&C Act, and the prohibition against interference with the practice of medicine. FDA may not go further, however, and undertake measures to ensure that physicians comply with the conditions of use in the labeling.

For example, if FDA determines that pregnant women should not take a particular drug, it may include such a warning in the labeling. If FDA further believes that, as an added safety precaution, physicians should not prescribe the drug to a woman unless she has had a pregnancy test in the last two months, the FD&C Act may permit FDA to place a statement in the labeling warning physicians not to prescribe the drug to a woman unless that woman has had a pregnancy test in the previous two months. Similarly, if FDA believes that only physicians with certain specified training should prescribe the drug, FDA may also include a statement to this effect in the label. These suggestions and warnings become additional prescribed, recommended, or suggested conditions of use upon which the approval of the drug is based. Because the drug may be prescribed safely if physicians follow these conditions of use, FDA must approve the drug at this point.

Much as physicians are free to prescribe approved drugs off-label, they are also free to prescribe approved drugs outside of these other conditions of use. As discussed above, Congress has not granted FDA the authority to prevent this. It therefore cannot require the drug manufacturer to implement risk management programs to ensure compliance with these conditions. For example, it cannot require that manufacturers restrict distribution to physicians who have the training suggested in the labeling. Nor can it require a sticker program designed to prevent pharmacists from dispensing the drug absent proof that the suggested pregnancy test has

been performed. Again, to do so would effectively add grounds for denial of an NDA that do not exist in section 505(d), and would necessarily impede the practice of medicine.

Furthermore, FDA may not do indirectly what it cannot do directly. Because FDA may not force manufacturers to implement risk management tools, it also may not place in the labeling, as a condition of use, that physicians should not prescribe a given drug unless the manufacturer has certain risk management tools in place. Such a condition of use is designed not to provide physicians with information, but to prevent use of an approved drug by physicians outside of the conditions of use that FDA has deemed to be safe. Such a condition of use would, again, exceed FDA's limited authority under the FD&C Act and inappropriately interfere with the practice of medicine.

Risk management tools such as restrictions on distribution or use therefore can be employed only with the consent of the manufacturer. This is the only approach that is consistent with both the limited authority given to FDA under the FD&C Act, and the prohibition against FDA interference with the practice of medicine. Risk management programs voluntarily adopted by manufacturers do not conflict with the FD&C Act and do not result in interference by FDA in the practice of medicine. FDA and industry agree that in the vast majority of cases risk can be effectively minimized through labeling and other routine risk minimization tools. PhRMA's members will work with FDA to develop and implement risk management programs in those rare cases where rigorous programs are necessary to protect patient safety.

V. FDA's Subpart H Regulations Do Not Expand FDA's Authority

FDA's regulations at Subpart H do not authorize FDA to impose risk management restrictions without the consent of drug manufacturers. The Subpart H regulations provide two procedures under which FDA may grant accelerated approval to drugs for serious or life

threatening illnesses -- namely (1) FDA is authorized to approve a new drug based on surrogate endpoint data if the sponsor agrees to conduct and submit data from postmarketing studies, and (2) FDA may grant accelerated approval to "beneficial but highly toxic" drugs in exchange for post-approval distribution and use restrictions.[25] Post-approval distribution and use restrictions may include (a) restricting distribution to certain facilities or to physicians with special training or experience, or (b) conditioning distribution on the performance of specified medical procedures.[26] Thus, Subpart H is a voluntary program whereby manufacturers can receive accelerated approval of new drugs for serious or life threatening conditions in exchange for post marketing studies or distribution and use restrictions.

FDA has always recognized, as it must given the limitations to FDA's authority under the FD&C Act, that it may impose distribution restrictions on an approved new drug under Subpart H only with the consent of the drug's sponsor. In the preambles to both the proposed and final rules, FDA stated that a sponsor must elect to use accelerated approval and must agree to distribution and use restrictions requested by FDA before such restrictions may be imposed on an approved drug. For example, the preamble to the proposed rule states that restrictions imposed on the distribution or use of an accelerated approval drug "would be . . . agreed to by the manufacturer at the time of approval."[27] Similarly, the preamble to the final rule states that "because firms will not be forced to use the accelerated approval mechanism, applicants will

---

[25] *See* 21 C.F.R.§§ 314.510 and 314.520.

[26] *See* 57 Fed. Reg. 13237.

[27] *Id.*

most probably choose to take advantage of the program only where its use is expected to reduce net costs."[28]

Subpart H is therefore for accelerated approval of certain drugs intended to treat serious and life threatening conditions, in exchange for voluntary acceptance of conditions by the manufacturer.[29] This serves a useful purpose by permitting these important drugs to reach the marketplace more quickly than they otherwise would under the normal approval process, provided that the manufacturer agrees to certain postapproval conditions. Any attempt by the Agency to use Subpart H to impose such conditions on manufacturers, however, would exceed FDA's authority under the FD&C Act. Nothing in the statute gives the Agency the authority to impose conditions such as RiskMAP tools on drug manufacturers, under Subpart H or otherwise.

---

[28] 57 Fed. Reg. 58958. FDA stated in these preambles that it relied on sections 501, 502, 503, 505, and 701 of the FD&C Act for its authority to impose restrictions on distribution and use. *See* 57 Fed. Reg. 13237. These sections, however, do not authorize FDA to impose risk management restrictions absent voluntary agreement by drug sponsors under Subpart H. As has been discussed above, section 505 of the FD&C Act confers on FDA the authority to deny or withdraw an application only where no conditions of use can be put into the drug's labeling such that the drug can be safely used by physicians if those prescribed, recommended, or suggested conditions are followed. Sections 501, 502, and 503 of the FD&C Act do not expand on that authority. Section 701, by its terms, provides FDA with authority to issue regulations only so far as they promote the efficient enforcement of the FD&C Act. That provision does not authorize FDA to implement regulations that exceed authority conferred upon it by the statute.

[29] Indeed, the very structure of Subpart H makes clear that the program applies only to cases where the manufacturer is seeking accelerated approval of drugs treating serious or life-threatening conditions. The Subpart itself is titled "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses." 21 C.F.R. § 314, Subpart H. The first subsection of Subpart H, 21 C.F.R. § 314.500, sets forth the regulation's scope. It notes that Subpart H applies only to those drugs that have been studied for serious or life-threatening conditions. The remaining subsections, including those discussing restrictions to assure safe use (21 C.F.R. § 314.520) are subject to the qualifications set forth in the title of Subpart H and its scope.

VI. First Amendment Limitations

Separate and apart from the statutory limitations on risk management discussed above, the First Amendment also places important restrictions on the Agency's ability to impose risk management programs. Certain risk management tools discussed in the Risk Management Draft Guidances require drug manufacturers to engage in speech. For example, some targeted education and outreach tools may require that drug manufacturers speak by disseminating reminders and other prescribing recommendations to physicians. FDA must be mindful of First Amendment limitations in seeking to impose these speech obligations as part of its risk management policies.

The First Amendment protects "both the right to speak freely and the right to refrain from speaking at all."[30] In the non-commercial speech context, the right not to speak means that the government may not, absent special circumstances, require private speakers to convey particular messages against their will. In the commercial speech context, the First Amendment permits the government to compel commercial speakers to make such disclosures, but only as necessary to "dissipate the possibility of consumer confusion or deception."[31] Such required disclosures may include "additional information, warnings, and disclaimers, as are necessary to prevent its being deceptive."[32]

The Supreme Court has made clear that disclosure requirements in the commercial speech context remain subject to First Amendment scrutiny. Thus, in *Zauderer* v. *Office of Disciplinary Counsel*, the Court held that any required disclosure must be "reasonably

---

[30] *Wooley* v. *Maynard*, 430 U.S. 704, 714 (1977).

[31] *See In re R. M. J.*, 455 U.S. 191, 201 (1982).

[32] *Virginia State Bd. of Pharmacy* v. *Virginia Citizens Consumer Council, Inc.*, 425 U.S. 748, 772 n.24 (1976).

related to the State's interest in preventing deception of consumers."[33] Forced disclosure must not be "unjustified" or "unduly burdensome,"[34] and must be "appropriately tailored . . . against deception or confusion."[35]

In the context of risk management, the government's right to require disclosure to avoid consumer confusion or deception translates into an ability to require disclosure to avoid harm to patients that would occur if the required disclosure was not made. But the free speech rights guaranteed by the First Amendment require that "[t]he party seeking to uphold a restriction on commercial speech carries the burden of justifying it."[36] To justify forced disclosure in a risk management program, FDA "must demonstrate that the harms it recites are real," and not "mere speculation or conjecture" by the Agency.[37] Furthermore, FDA must demonstrate that the disclosure it wishes to mandate "will in fact alleviate [the harms] to a material degree."[38]

The Court's First Amendment jurisprudence also makes clear that the First Amendment permits only disclosures of factual information. The Court has upheld forced disclosure in the commercial speech context where the disclosure was of "purely factual and uncontroversial information."[39] FDA therefore may not, consistent with the First Amendment, go further to force manufacturers to make statements (in labeling, education and outreach programs, or otherwise) that lack factual support or that constitute opinion. For example, FDA is

---

[33] 471 U.S. 626, 650-51 (1985).

[34] *See id.* at 651.

[35] *Ibanez* v. *Florida Dep't of Business and Prof. Reg.*, 512 U.S. 136, 146 (1994).

[36] *Edenfield* v. *Fane*, 507 U.S. 761, 770 (1993).

[37] *See id.*

[38] *See id.*

[39] *Zauderer*, 471 U.S. at 651.

free to require warnings in a drug's labeling against use of the drug in certain patient populations, but must first demonstrate that data support the conclusion that such use presents a significant risk of harm.

When considering its final policy on risk management, and particularly those tools that involve speech (such as labeling, physician reminder programs, or patient education programs), FDA must be mindful of these First Amendment limitations. FDA bears the burden of demonstrating that any required disclosure is reasonably related to the State's interest in avoiding consumer deception or confusion, and that real evidence supports the need for the disclosure. The First Amendment does not permit FDA to use risk management to force manufacturers to be FDA's voice for expressing its mere opinions. These First Amendment considerations apply in addition to the important statutory limitations that exist on FDA's authority to impose risk management plans.

VII. Conclusions

The FD&C Act prohibits FDA from imposing risk management programs on manufacturers as a condition of approval (or avoidance of withdrawal) of a prescription drug. Congress intended, and provided in the statute, that FDA would make the initial determination of the conditions of use, if any exist, under which a prescription drug may be safely administered, and place those conditions of use in the approved labeling. It is then to physicians, relying upon their training, experience, and intimate familiarity with their patients, to make the final determinations of which prescriptions, recommendations, and suggestions in the approved labeling apply in a given situation for a given patient.

FDA has no authority to go beyond the labeling and impose risk management tools such as restrictions on distribution. To do so would violate the FD&C Act, fly in the face

of longstanding FDA policy against interference in the practice of medicine, possibly violate the First Amendment, and potentially impede optimal health care decisions for patients and the advancement of medical science as a whole. Thus, risk management programs that extend beyond labeling must be voluntarily adopted by manufacturers, in consultation and cooperation with the Agency. PhRMA's members intend to work closely with the Agency to implement these programs where they are necessary to protect patient safety.